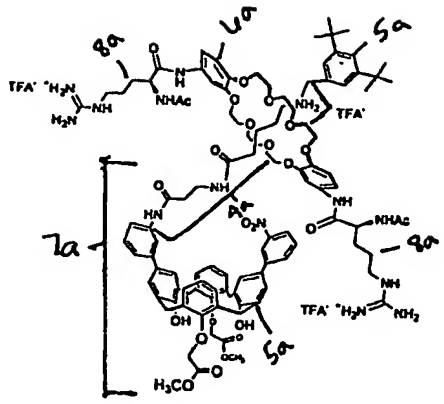
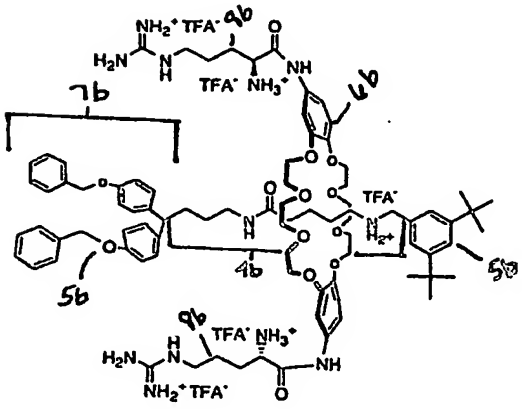
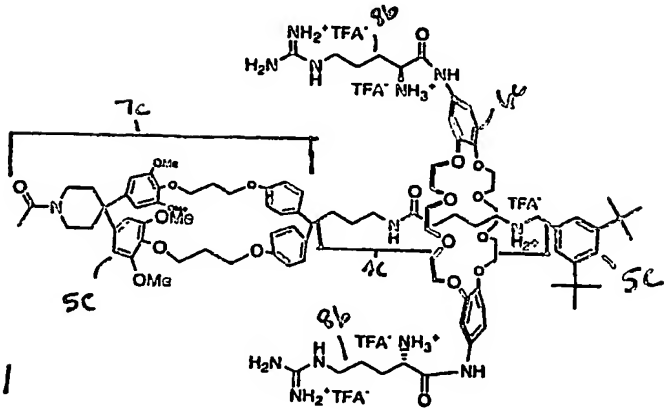


1



2



3

Figure 1

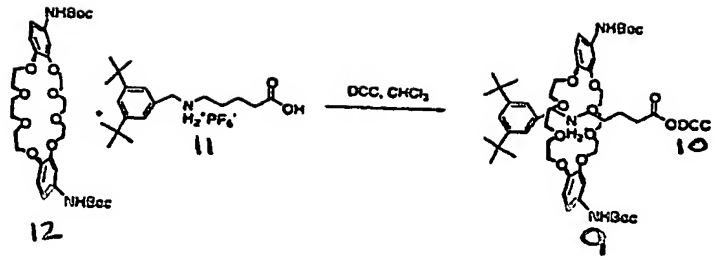
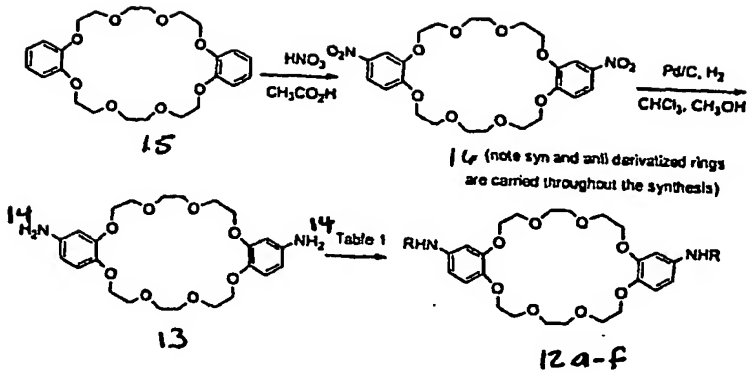

NHBoc
NHBoc
12
N
H2+PF6-
OH
11
DCC, CHCl3
NHBoc
N
H2+
ODCC
10
NHBoc
9

Figure 2



Synthesis of Derivatized Crown Ethers

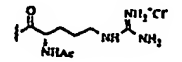
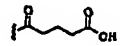
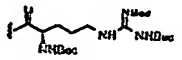
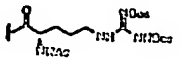
Cmpd	Reagent	R	yield
12a	BOP, N-Ac-ArgOH, DIEA, DMF		50%
12b	(1)  , Et3N (2) HCl		78%
12c	CDI, (Boc)2ArgOH, CHCl3, reflux		55%
12d	CDI, Ac(Boc)2ArgOH, CHCl3, reflux		60%
12e	(CF3CO)2O, pyridine, CH2Cl2		90%
12f	From 6 (Boc)2O, H2, Pd/C, DMF		90%

Figure 3

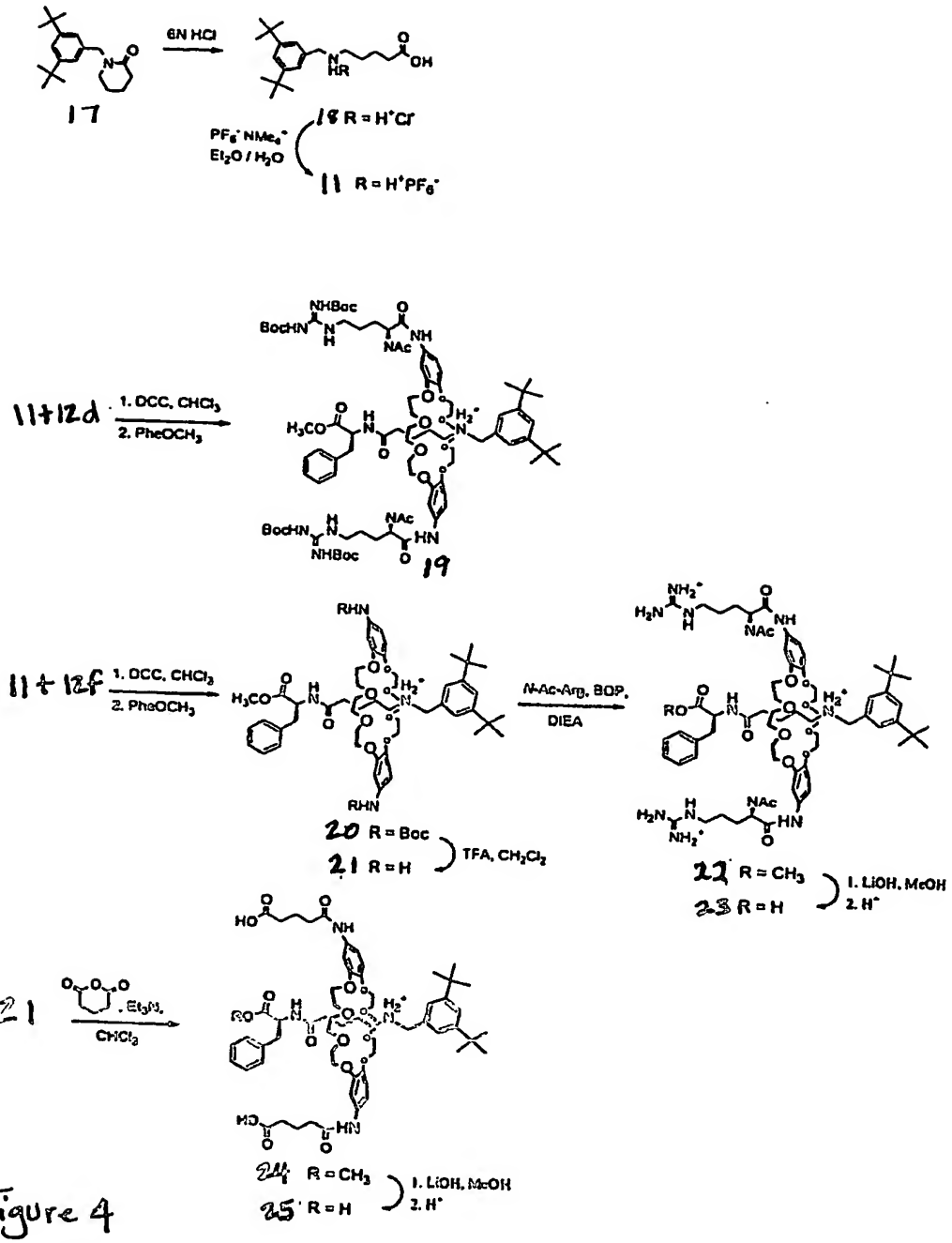
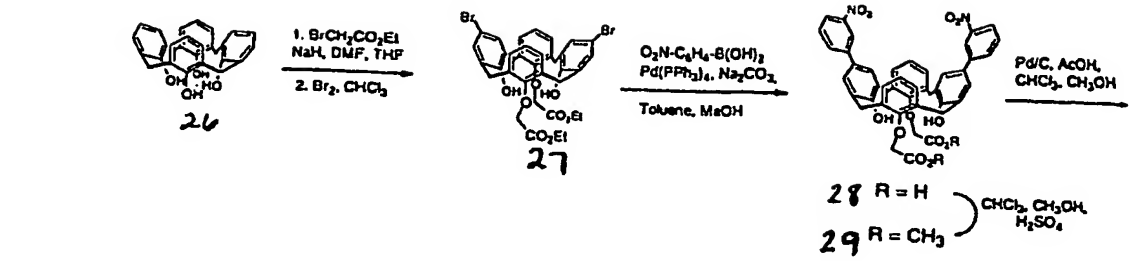
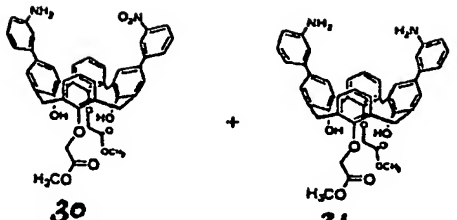

6N HCl
17
18 R = H+Cl-
PF6- NMe4+
Et2O / H2O
11 R = H+PF6-
11+12d
1. DCC, CHCl3
2. PheOCH3
19
11+12f
1. DCC, CHCl3
2. PheOCH3
N-Ac-Arg, BOP,
DIEA
20 R = Boc
21 R = H
TFA, CH2Cl2
22 R = CH3
23 R = H
1. LiOH, MeOH
2. H+
21
Et3N,
CHCl3
24 R = CH3
25 R = H
1. LiOH, MeOH
2. H+

Figure 4





Partial reduction: 7: 8: 3 in a ratio of 1 : 2. 7 : 4.3

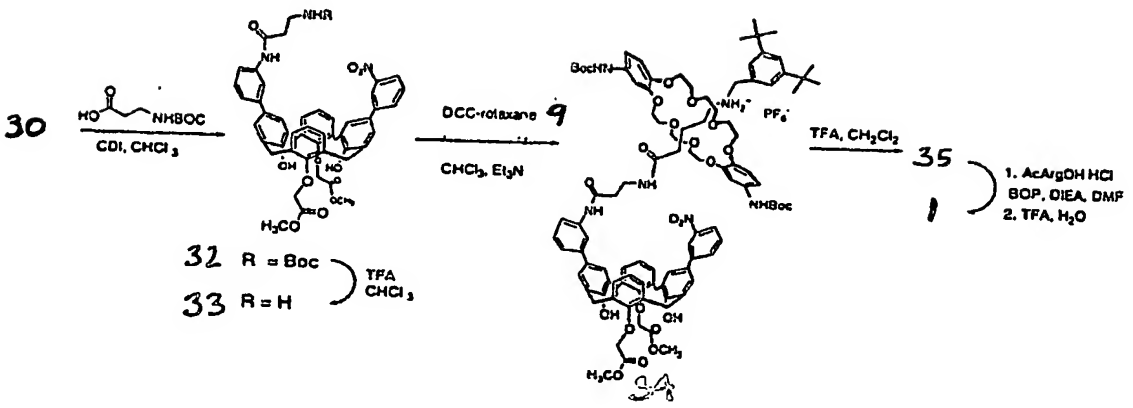


Figure 5

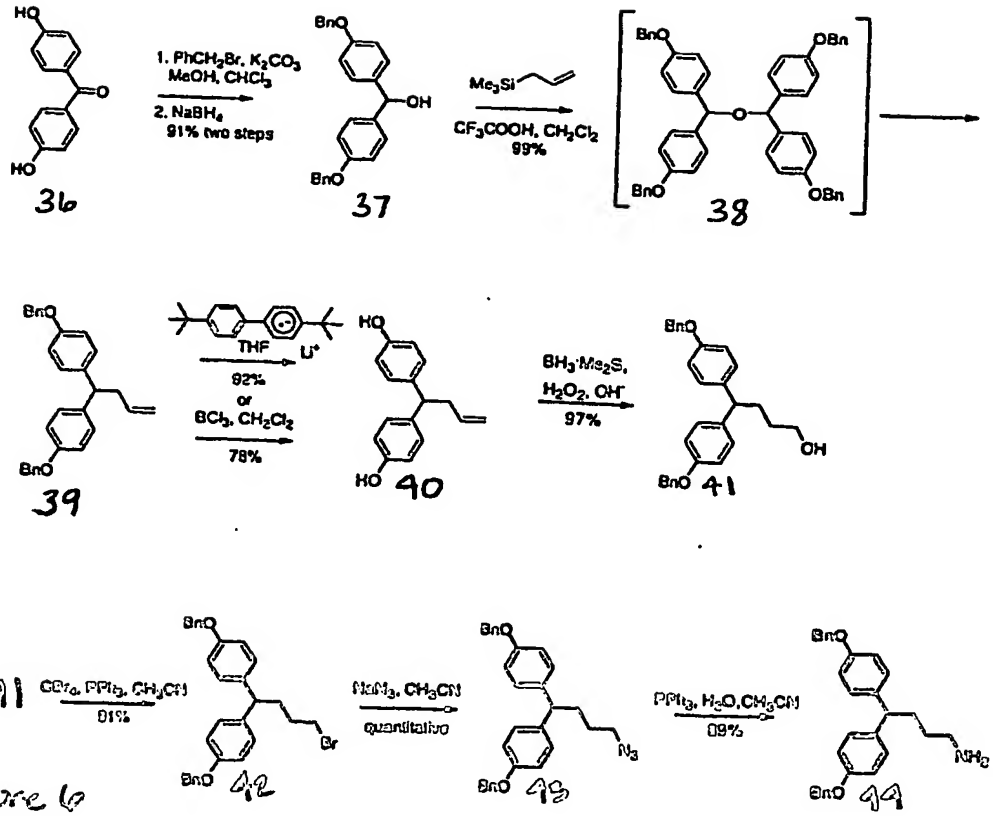

HO
O
HO
36
1. PhCH2Br, K2CO3
MeOH, CHCl3
2. NaBH4
91% two steps
BnO
OH
BnO
37
Me3Si
CF3COOH, CH2Cl2
99%
BnO
OBn
O
BnO
OBn
38
BnO
BnO
39
THF
Li+
92%
or
BCl3, CH2Cl2
78%
HO
HO
40
BH3·Me2S,
H2O2, OH-
97%
BnO
OH
BnO
41
41
CBr4, PPh3, CH3CN
91%
BnO
Br
BnO
42
NaN3, CH3CN
quantitative
BnO
N3
BnO
43
PPh3, H2O, CH3CN
89%
BnO
NH2
BnO
44

Figure 6

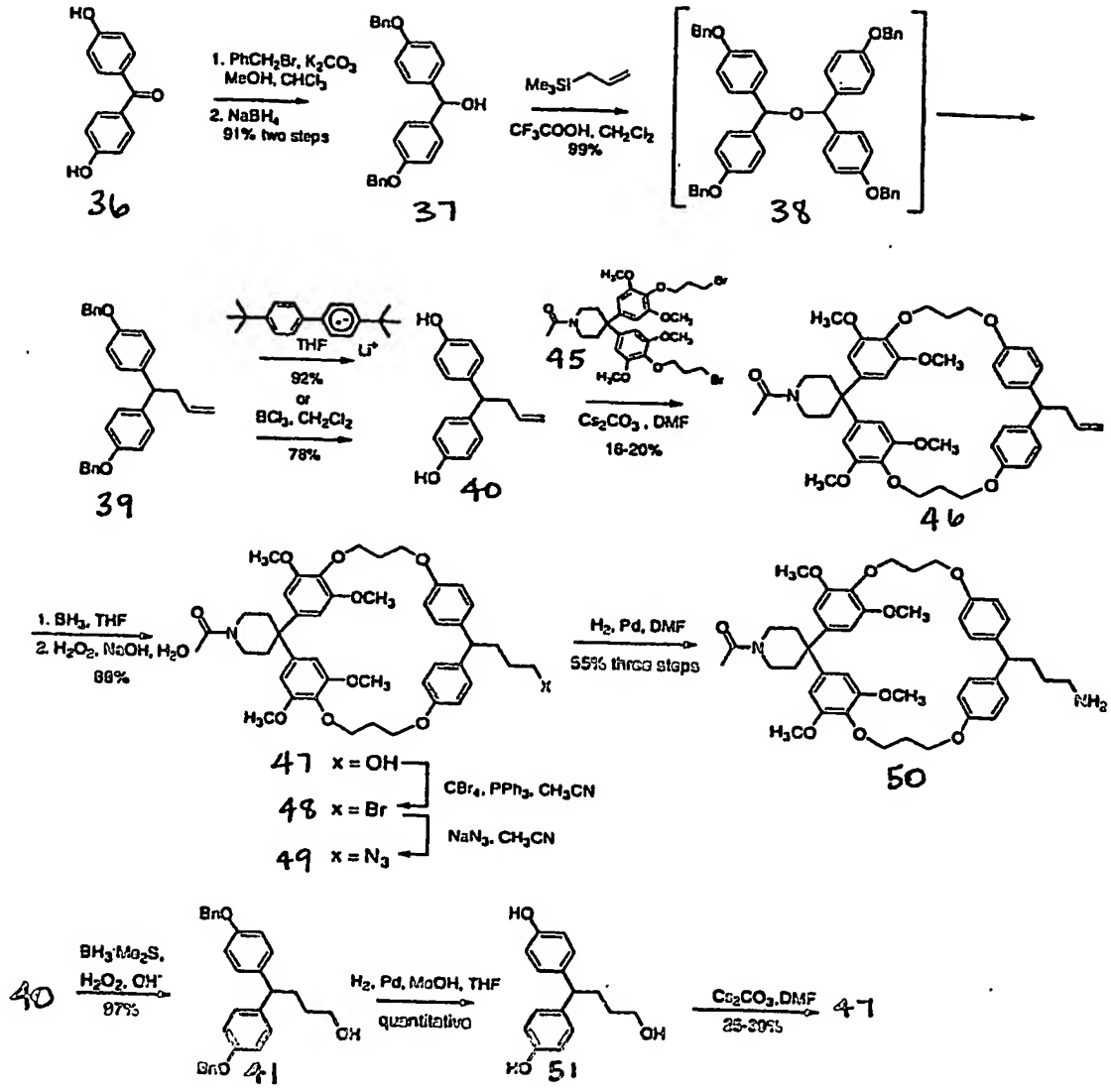

1. PhCH2Br, K2CO3, MeOH, CHCl3
2. NaBH4
91% two steps
Me3Si
CF3COOH, CH2Cl2
99%
THF
Li+
92%
or
BCl3, CH2Cl2
78%
Cs2CO3, DMF
16-20%
1. BH3, THF
2. H2O2, NaOH, H2O
88%
H2, Pd, DMF
55% three steps
47 x = OH
48 x = Br
49 x = N3
CBr4, PPh3, CH3CN
NaN3, CH3CN
BH3·Me2S,
H2O2, OH-
97%
H2, Pd, MeOH, THF
quantitative
Cs2CO3, DMF
25-30%

Figure 7

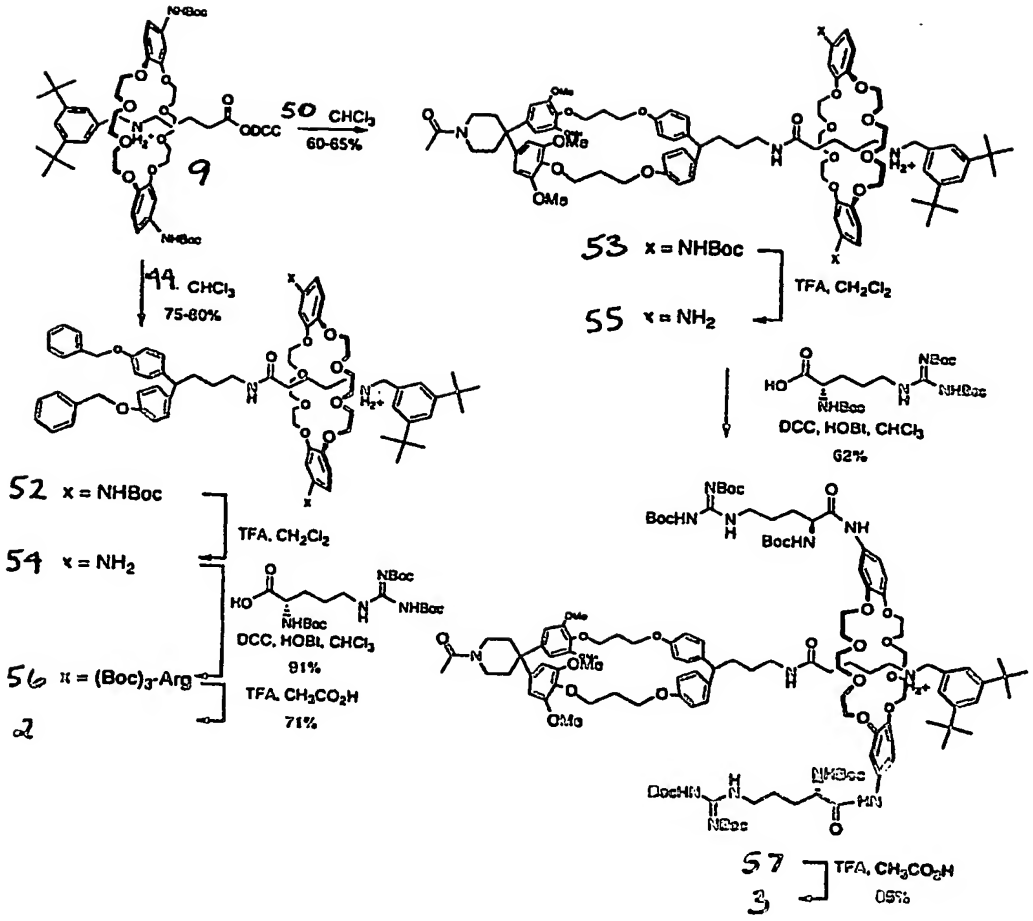
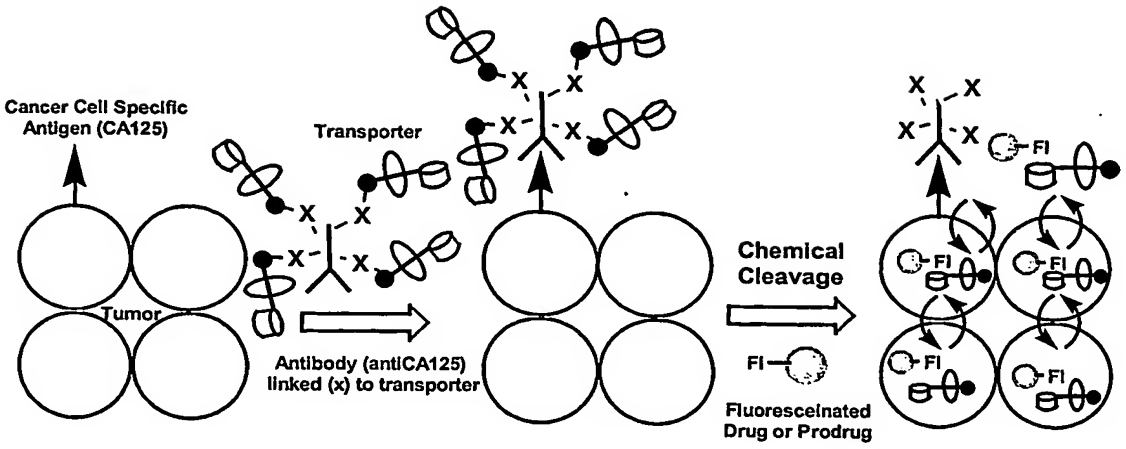

50 CHCl3
60-65%
9
49 CHCl3
75-80%
53 x = NHBoc
TFA, CH2Cl2
55 x = NH2
DCC, HOBt, CHCl3
62%
52 x = NHBoc
TFA, CH2Cl2
54 x = NH2
DCC, HOBt, CHCl3
91%
56 x = (Boc)3-Arg
TFA, CH2CO2H
71%
2
57
TFA, CH3CO2H
3
95%

Figure 8

FIGURE 9


Cancer Cell Specific Antigen (CA125)
Transporter
Tumor
Antibody (antiCA125) linked (x) to transporter
Chemical Cleavage
Fl
Fluoresceinated Drug or Prodrug
X
Fl

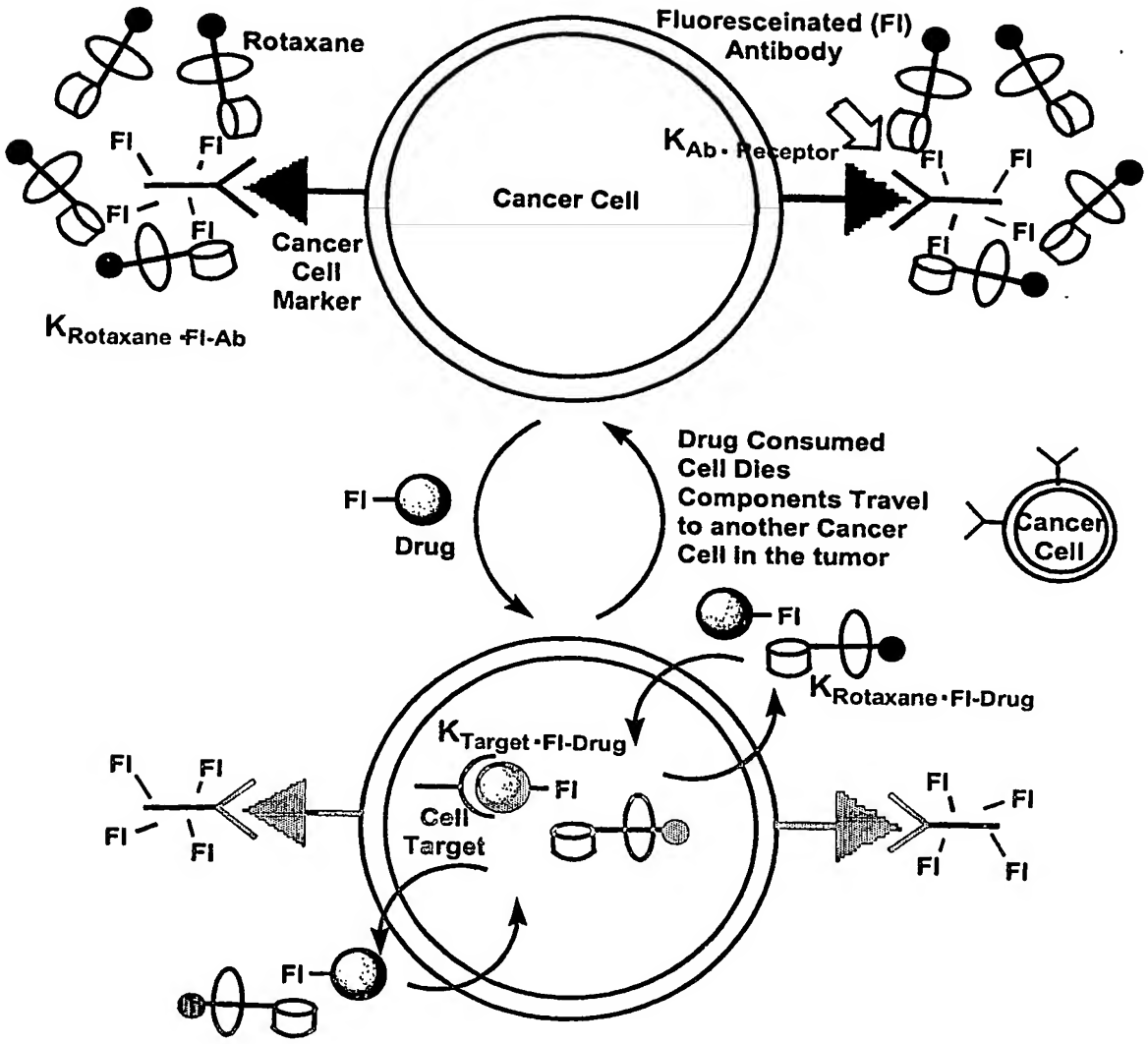

Rotaxane
Fl
Fl
Fl
Fl
Fl
Cancer Cell Marker
$K_{Rotaxane \cdot Fl\text{-}Ab}$
Fluoresceinated (Fl) Antibody
$K_{Ab \cdot Receptor}$
Cancer Cell
Drug Consumed
Cell Dies
Components Travel
to another Cancer
Cell in the tumor
Cancer Cell
Drug
$K_{Rotaxane \cdot Fl\text{-}Drug}$
$K_{Target \cdot Fl\text{-}Drug}$
Cell Target

FIGURE 10

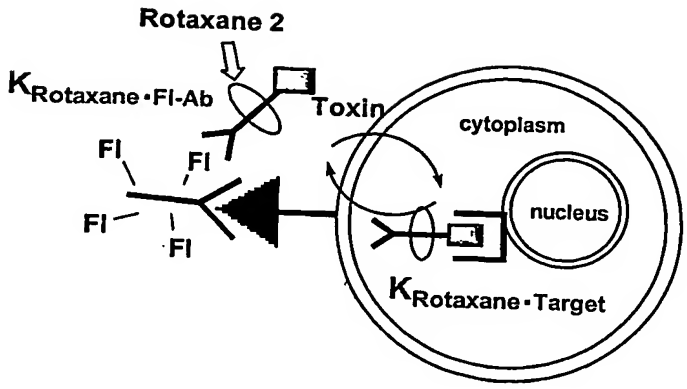
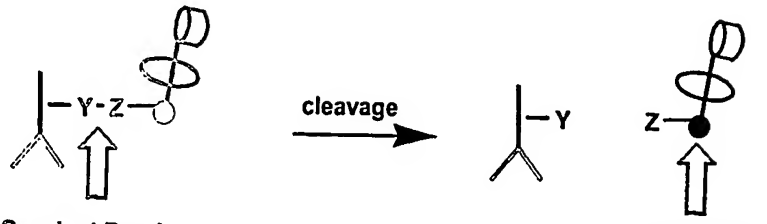

Rotaxane 2
$K_{Rotaxane \cdot Fl\text{-}Ab}$
Toxin
cytoplasm
Fl
Fl
Fl
Fl
nucleus
$K_{Rotaxane \cdot Target}$

FIGURE 11



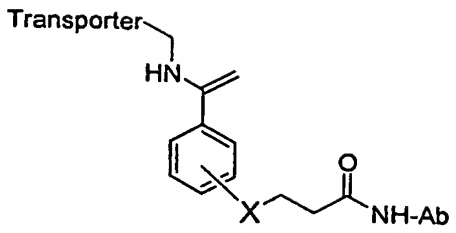
Covalent Bond

1. stable enough to synthesize the conjugate
2. breaks after the antibody binds the tumor
3. best to have a triggering mechanism (light or pH)

Transporter

1. will be derivatized with Z
2. still needs to be a transporter
3. prefer the tumor over serum
4. not toxic once cancer cells are killed

FIGURE 12



o, m, or p disubstituted ring
X can be C, N, O

FIGURE 13

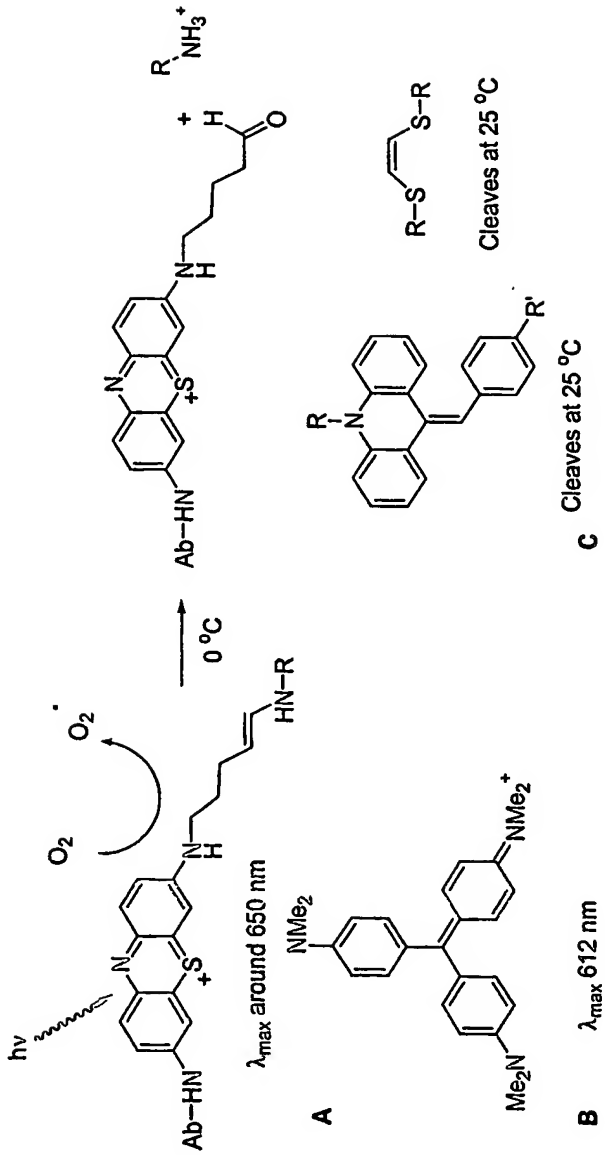

hν
O_2
$O_2^{\cdot}$
Ab–HN
HN–R
λ_{max} around 650 nm
A
0 °C
Ab–HN
$R–NH_3^+$
B
λ_{max} 612 nm
R–S
S–R
Cleaves at 25 °C
C
Cleaves at 25 °C

Figure 14.

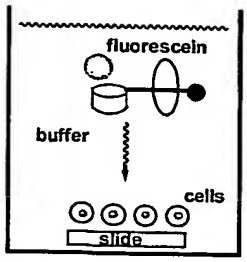


FIGURE 15

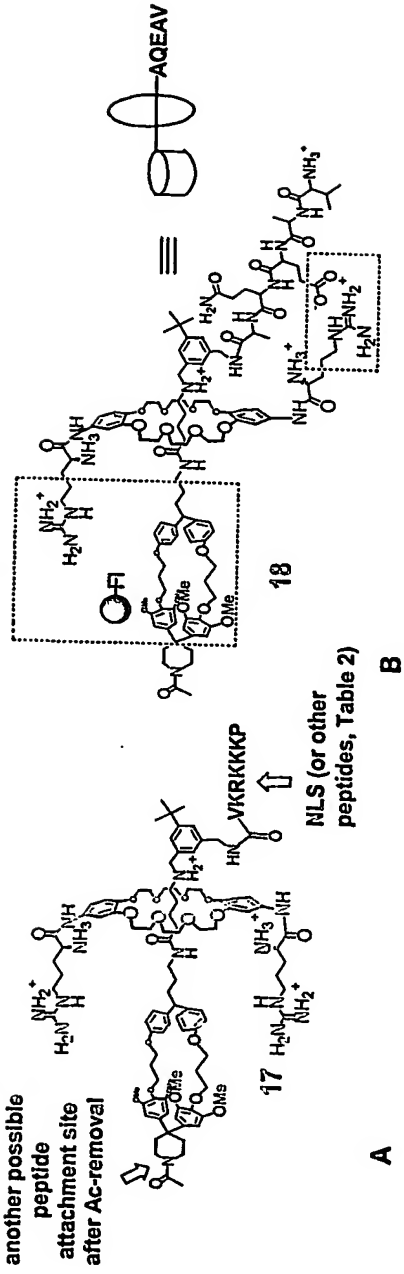

AQEAV
another possible peptide attachment site after Ac-removal
VKRKKKP
NLS (or other peptides, Table 2)
17
18
A
B

Figure 16.

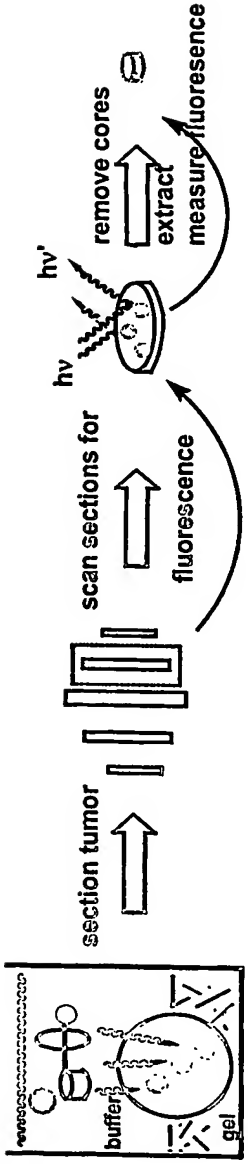

section tumor
scan sections for
fluorescence
hv
hv'
remove cores
extract
measure fluoresence
buffer
gel

Figure 17.

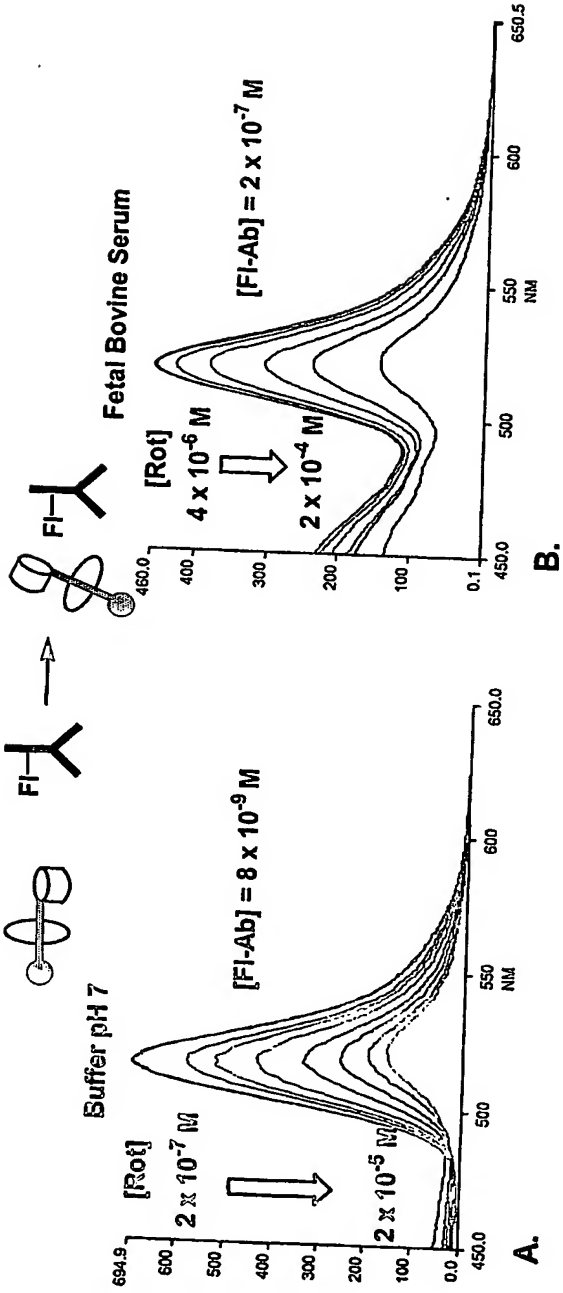

Buffer pH 7
Fetal Bovine Serum
Fl
[Rot]
2 x 10-7 M
2 x 10-5 M
[Fl-Ab] = 8 x 10-9 M
[Rot]
4 x 10-6 M
2 x 10-4 M
[Fl-Ab] = 2 x 10-7 M
NM
A.
B.

Figure 18.

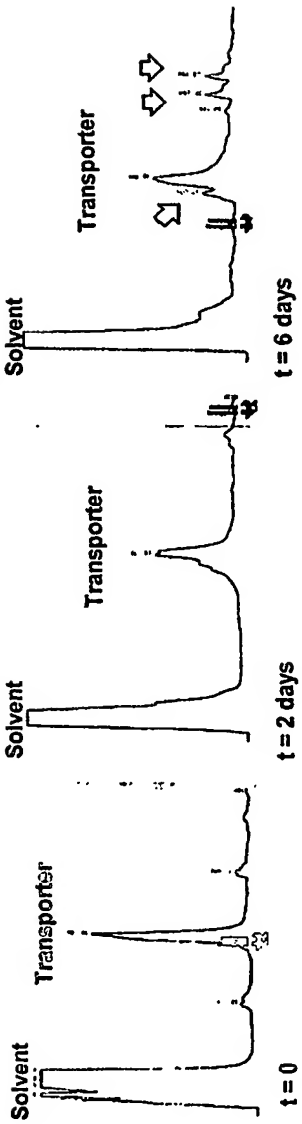

Solvent
Transporter
t = 0
Solvent
Transporter
t = 2 days
Solvent
Transporter
t = 6 days

Figure 19.

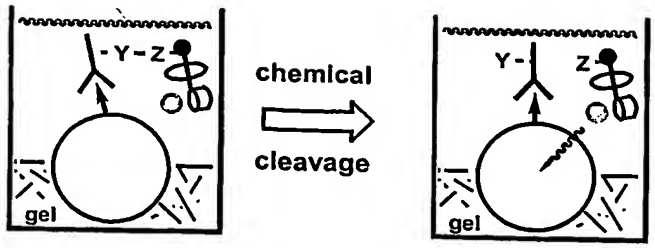


Figure 20.

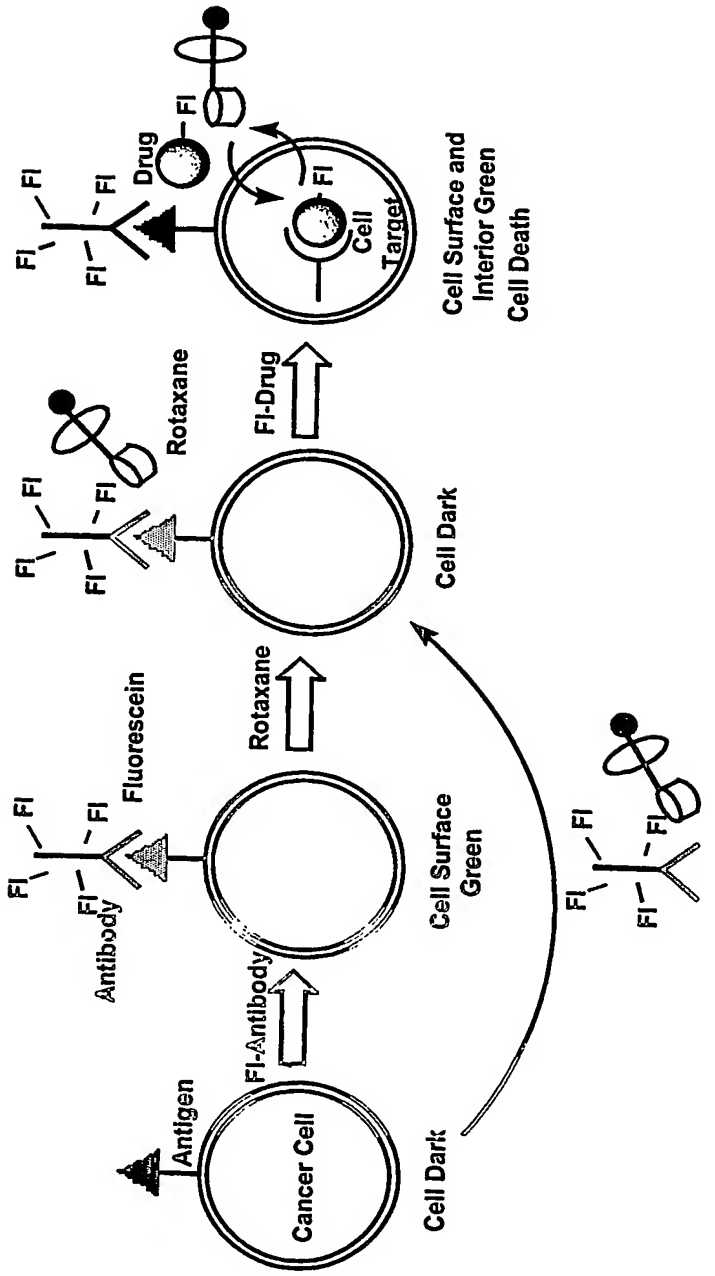
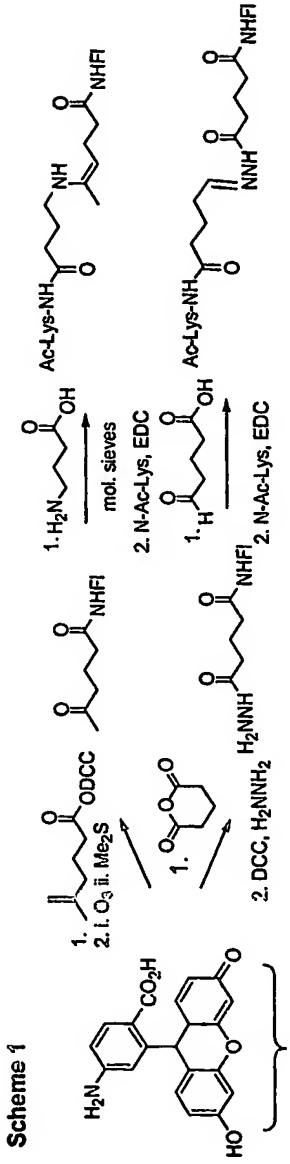

Antigen
Cancer Cell
Fl-Antibody
Antibody
Fl
Fluorescein
Cell Surface
Green
Rotaxane
Cell Dark
Rotaxane
Fl-Drug
Drug
Cell
Target
Cell Surface and
Interior Green
Cell Death
Cell Dark

FIGURE 21

Figure 22.


Scheme 1
Fl
1. 2. i. O_3 ii. Me_2S
ODCC
1.
2. DCC, H_2NNH_2
H_2NNH
NHFl
1. H_2N
mol. sieves
2. N-Ac-Lys, EDC
Ac-Lys-NH
NH
NNH

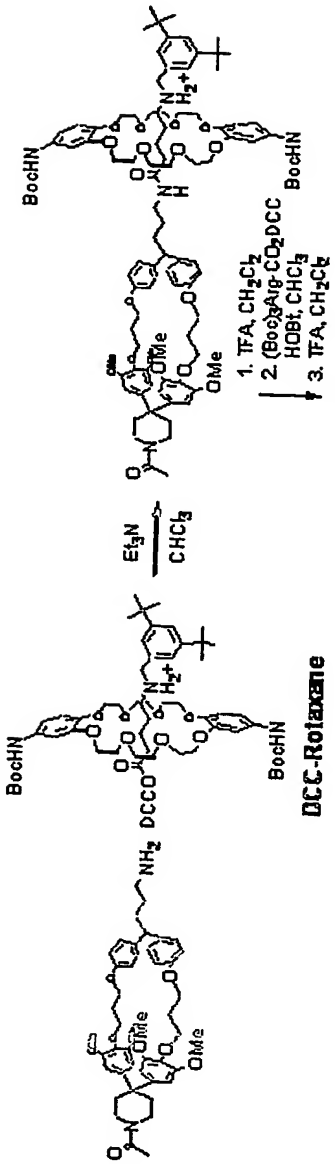

BocHN
BocHN
OMe
OMe
1. TFA, CH2Cl2
2. (Boc)3Arg-CO2DCC
HOBt, CHCl3
3. TFA, CH2Cl2
1
Et3N
CHCl3
DCC-Rotaxane
BocHN
BocHN
DCCO
NH2
OMe
OMe

Figure 23.

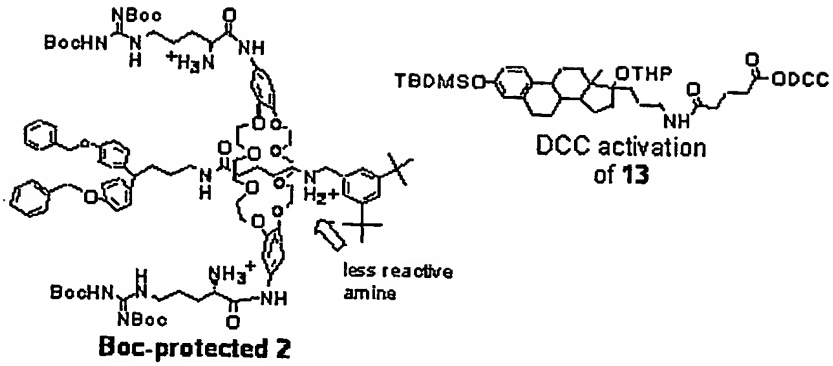

NBoc
BocHN
NH
TBDMSO
OTHP
ODCC
DCC activation
of 13
less reactive
amine
Boc-protected 2

Figure 24.

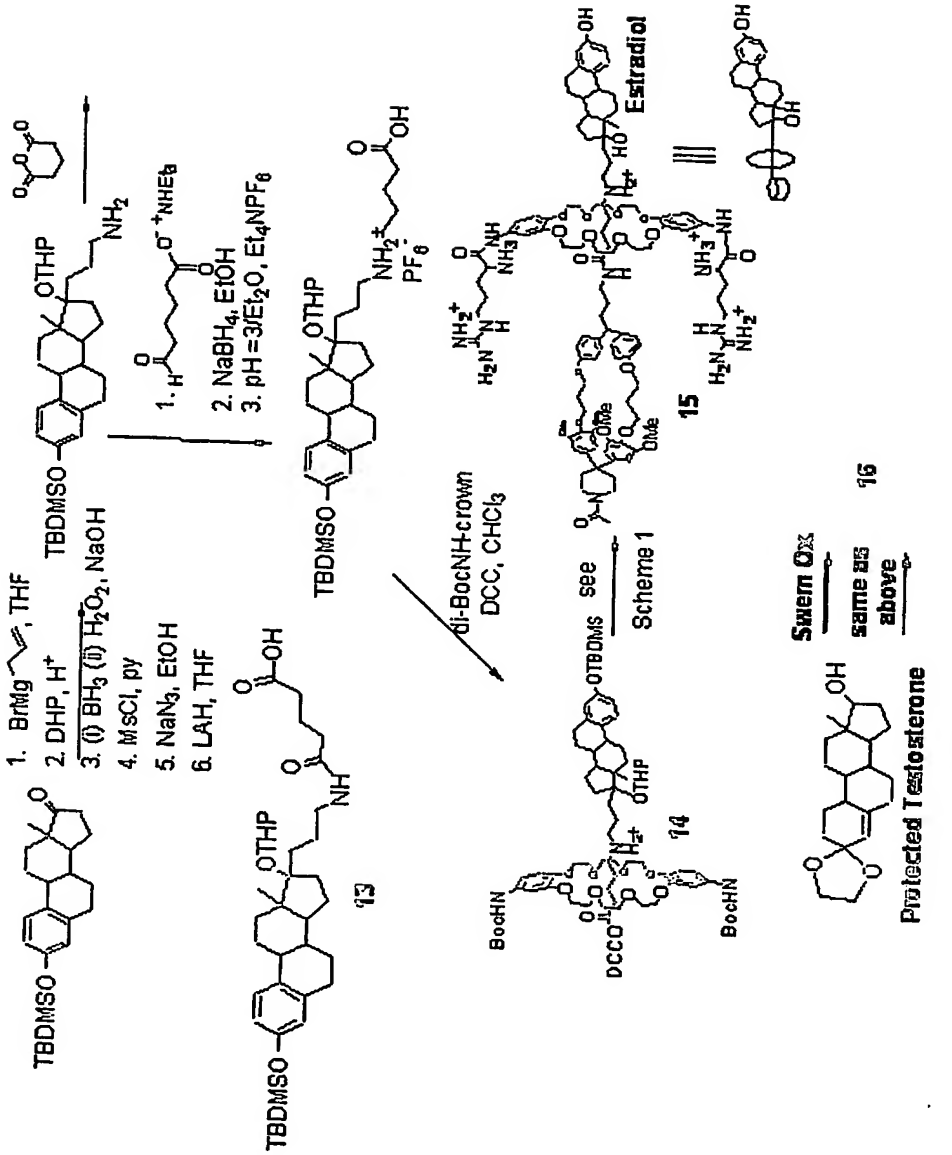

1. BrMg, THF
2. DHP, H+
3. (i) BH3 (ii) H2O2, NaOH
4. MsCl, py
5. NaN3, EtOH
6. LAH, THF
TBDMSO
OTHP
NH2
13
1. NHEt3
2. NaBH4, EtOH
3. pH=3/Et2O, Et4NPF6
NH2+ PF6-
OH
di-BocNH-crown
DCC, CHCl3
see Scheme 1
14
15
Estradiol
Swern Ox
same as above
16
Protected Testosterone

Figure 25.

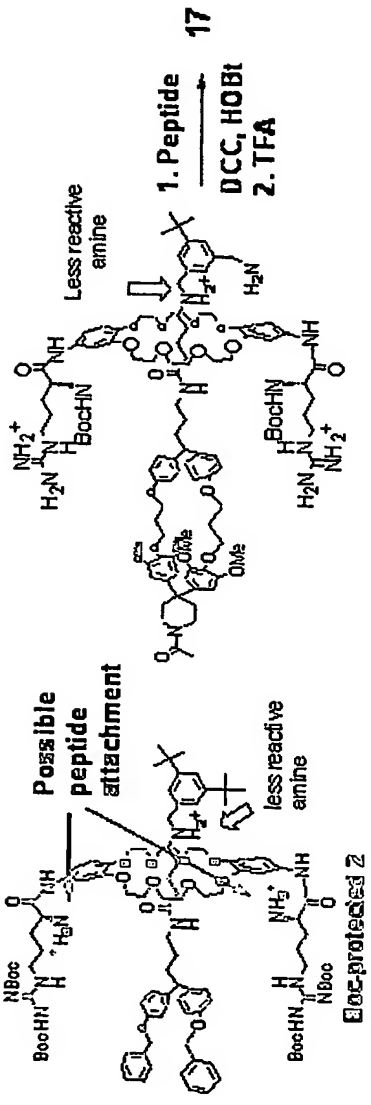

Possible peptide attachment
less reactive amine
Less reactive amine
1. Peptide
DCC, HOBt
2. TFA
17
Boc-protected 2

Figure 26.

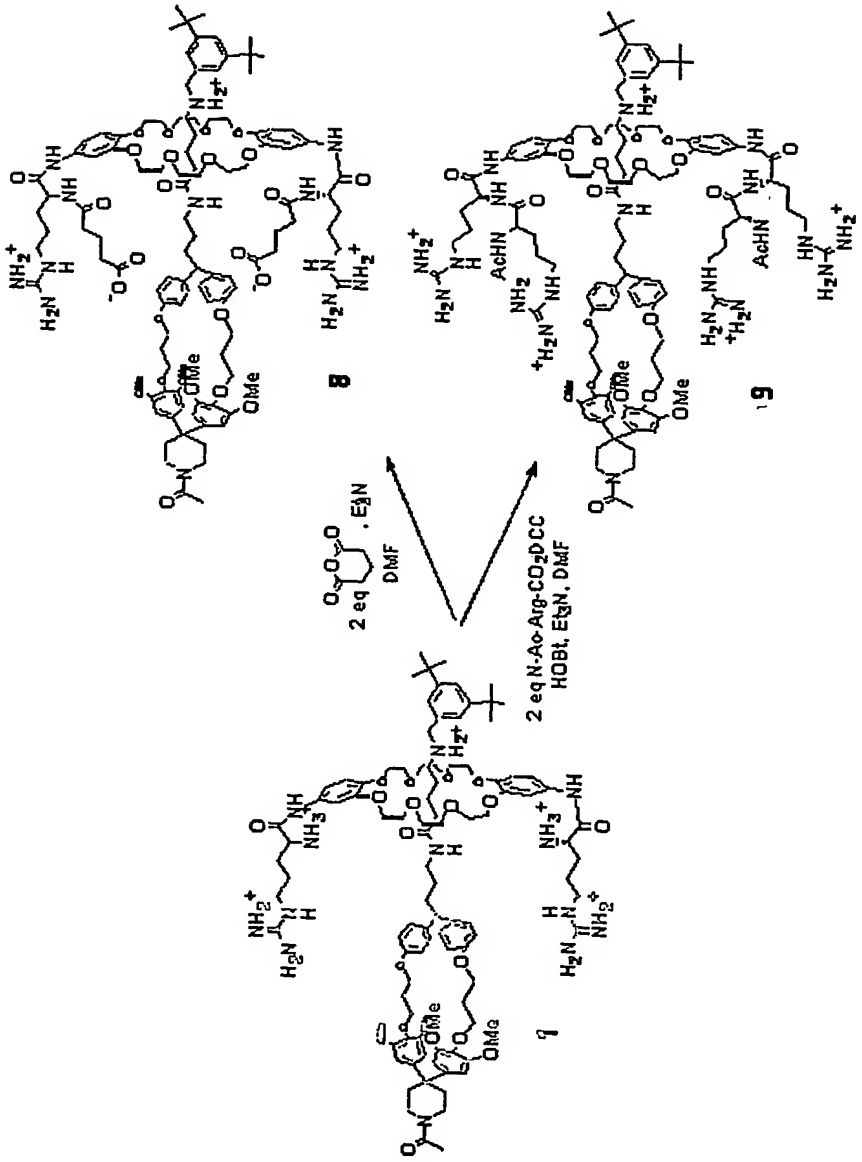


Figure 27.

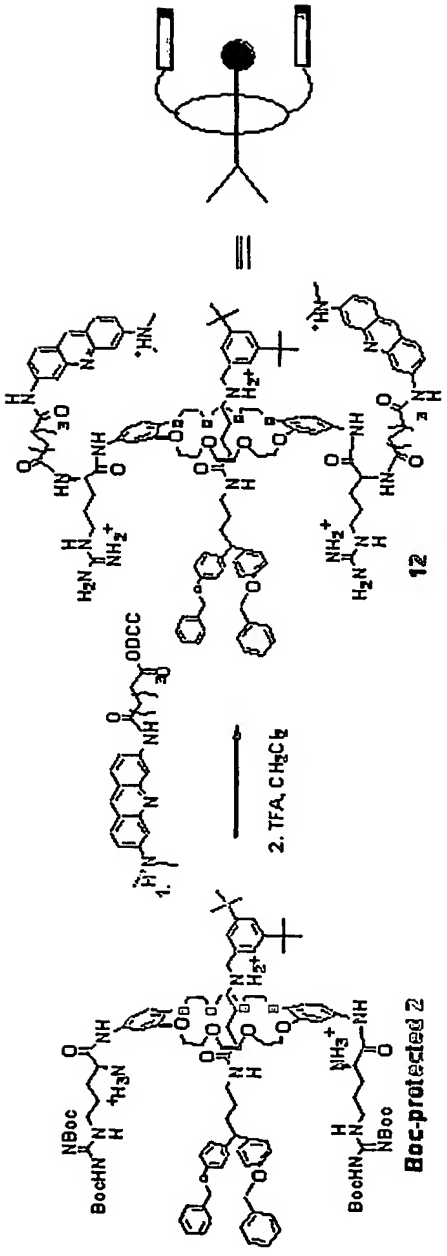


Figure 28.

Figure 29.